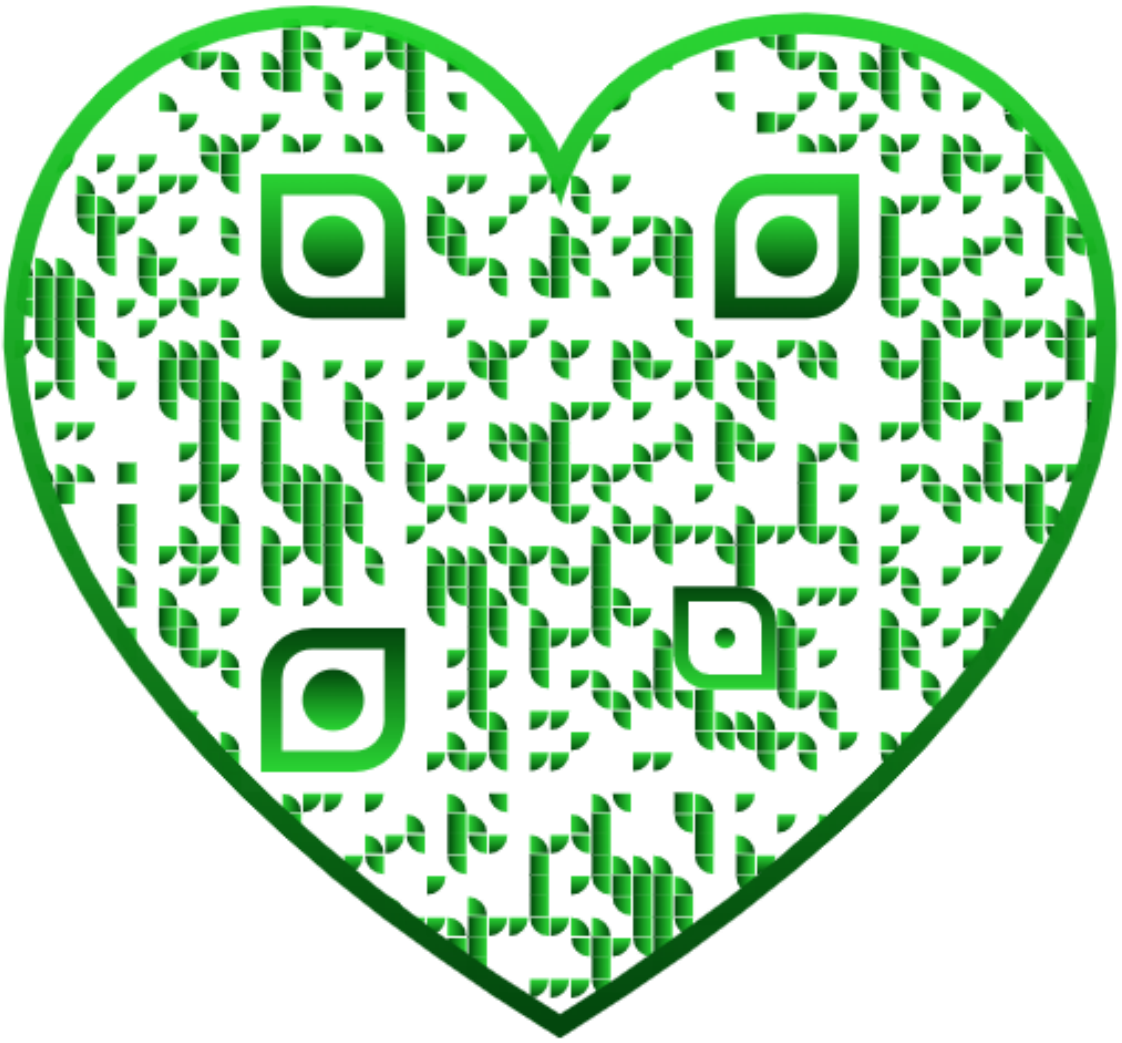
5. Liquid Dosage Forms

- **Solutions**
- **Disperse Systems: Suspensions and Emulsions**



Solutions

- Formulation considerations
- Manufacturing processes
- Quality evaluations

- Liquid pharmaceuticals (solutions) are generally preferred:
  - Ease of administration to those individuals who have difficulty of swallowing solid dosage forms.
  - More rapidly and efficiently absorbed than the **same** amount of drug administered in a tablet or capsule.
    - A drug administered in solution is immediately available for absorption.

...

- Solutions formulation poses many technical problems to the industrial pharmacist;
  - Some drugs are inherently unstable,
  - Special techniques are required to solubilize poorly soluble drugs,
  - Difficult to satisfy the requirements of pharmaceutical elegance with regard to taste, appearance, and viscosity.

Solutions, Formulation considerations

- The successful formulation of solution formulations requires a skill to identify;
  - Solubility and stability factors
  - Flavoring and other organoleptic factors

...

1. Solubility

- Solubility depends on the nature and intensity of the forces present within and between **solute** and **solvent**.

- Solubility of the drug of interest should be determined in a solvent that is similar to the one intended for use in the final product.

- Factors affecting solubility:
  - Temperature
  - pH
  - Co-solvency
  - Dielectric constant
  - Solubilization (Micellization)
  - Complexation
  - Hydrothrophy
  - Chemical modification of the drug

...

2. Preservation

- Clinical complications arising from microbial contamination of liquid products
- Tightened regulatory and compendial limits
- Microbial contaminations
  - Health hazard
  - Product stability

- Sources of contamination
  - Raw materials
  - Processing containers and equipments
  - Manufacturing environment
  - Operators
  - Packaging materials
  - The user

...

- An ideal preservative
  - Effective against broad spectrum of microorganisms
  - Must physically, chemically, and microbiologically stable
  - None toxic, none sensitizing, adequately soluble, compatible, acceptable (taste and odor)
- Combination of two or more preservatives may be required to achieve these properties

...

- Four categories of preservatives

    1. Acidic
    2. Neutral
    3. Mercurial
    4. Quaternary ammonium compounds

Class	*Usual Concentration (%)*
Acidic	
Phenol	0.2–0.5
Chlorocresol	0.05–0.1
O-phenyl phenol	0.005–0.01
Alkyl esters of parahydroxybenzoic acid	0.001–0.2
Benzoic acid and its salts	0.1–0.3
Boric acid and its salts	0.5–1.0
Sorbic acid and its salts	0.05–0.2
Neutral	
Chlorbutanol	0.5
Benzyl alcohol	1.0
β-phenylethyl alcohol	0.2–1.0
Mercurial	
Thimerosal	0.001–0.1
Phenylmercuric acetate and nitrate	0.002–0.005
Nitromersol	0.001–0.1
Quaternary Ammonium Compounds	
Benzalkonium chloride	0.004–0.02
Cetylpyridinium chloride	0.01–0.02

...

3. Subjective product characteristics

- "Pharmaceutical elegance" can't be quantitatively measured.
- The value of a pharmaceutical preparation is measured by its medical significance, and commercial success
  - Achieved with products that are **convenient to use** and receive **patient acceptance**.

...

4. Sweetening agents

Sucrose

- Long history of use
- Soluble in aqueous media
- Available in highly purified form at reasonable cost
- Chemically and physically stable at wider range of pH (4 to 8)
- **Problem**: Crystallization

...

Liquid glucose

- Obtained by partial hydrolysis of starch with strong acid
- In addition to its **sweetening** effect, it imparts characteristic odor and **flavor** (similar to honey and molasses)
- Better than the naturally occurring sweeteners (honey and molasses)

...

Saccharin

- Used to supplement sugars and polyols
- 250 to 500 times as sweet as sucrose
- But, it has bitter after taste, if not properly used in the formula

...

Aspartame

- Relatively newly approved synthetic sweetener
- It is a methyl ester of aspartic acid and phenyl alanine
- About 200 times more sweeter than sucrose
- Has no after taste of saccharine
- Stability in aqueous medium is pH and temperature dependent

...

5. Viscosity control

- It is sometimes desirable to increase the viscosity of a liquid either to improve palatability or improve pourability.
- This can be achieved either by:
  - Increasing sugar concentration
  - Incorporate viscosity controlling agents

...

- Methyl cellulose and carboxymethyl cellulose are available in different viscosity grades
  - CMC can be used in solutions containing high concentration of alcohol (about 50%) without precipitating.
  - CMC precipitate with multivalent metal ions forming insoluble salts.
  - MC is devoid of this, but can be salted out in concentration of electrolytes exceed certain limits
  - The polymers may form complexes.

...

6. Flavors

- Selection and evaluation of a flavorant is very important
- Four basic tastes: Salty, Bitter, Sweet, and Sour
  - Combination of flavors needed to mask these tastes.
- Menthol and chloroform are used as flavor adjuncts
  - They impart flavor and odor, and have mild anesthetic (**desensitization**) effect

...

- Monosodium glutamate has been widely used to enhance natural flavors
  - Effective to reduce metallic tastes, and bitterness and aftertaste of preparations.
- Final flavor selection must result from a trial and error approach.
  - But, careful of taste fatigue

Taste Sensation	*Recommended Flavor*
Salt	Butterscotch, maple, apricot, peach, vanilla, wintergreen mint
Bitter	Wild cherry, walnut, chocolate, mint combinations, passion fruit, mint spice, anise
Sweet	Fruit and berry, vanilla
Sour	Citrus flavors, licorice, root beer, raspberry

...

7. Appearance

- Overall appearance of pharmaceutical products depends primarily on their color and clarity.
- A purification step invariably required to achieve max clarity
- Removal of particulate matter "**Polishing**" may be required.

...

- Polishing of the final product mat be achieved by:
  - Settling and subsequent decantation
  - Centrifugation
  - Filtration
- Filtration is practical for large volume liquids.

...

8. Stability

- Chemical stability
  - Chemical instability of drugs is invariably magnified in solution
  - Need rapid and accurate stability predictions
    - This is possible with homogeneous systems but may be risky with heterogeneous systems.

- Physical stability
  - In terms of viscosity, color, clarity, taste, and odor
  - Should be evaluated **subjectively** and **objectively**
    - During subjective evaluation, a freshly prepared sample should be used as a reference standard.
    - For objective evaluation measurements should be made, e.g. Color (by spectrophotometer), Clarity (by light scattering)

Solutions, Manufacturing processes

- Basic principles of solution preparation remains the same regardless of volume
- Solubility of the solute at equilibrium is independent of the manner solution is made.
- The rate a which equilibrium is achieved, however, depends on the manufacturing procedure.

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1. Raw materials

- Specifications for raw materials shall meet:
  - Identity
  - Purity
  - Uniformity
  - Freedom from excessive microbial contamination

...

- Additional processing may be required before manufacturing (like particle size, and freedom from microorganisms)
- Water is an important constituent in a liquid products
  - USP requirements for purified water??
  - Different techniques to improve microbial purity of the water supply: Reverse osmosis, UV sterilization, Membrane filtration
  - Constant circulation in piping systems that have no “dead ends”

- During using UV sterilization for water treatment
  - Flow rate of water should not exceed sterilizing capacity
  - A filter should be used down stream to remove dead microorganisms and particulate matter.

...

2. Equipment

- Mixing tanks with means of Agitation, Measuring devices, and Filtration system are used.
- The tanks also have system for bulk material handling
- Tanks for mixing and holding
- The difference between holding and filling line shall be kept minimum to minimize risk of contamination.

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- All lines and systems should be easy to disassemble, clean and sanitize.
- Tanks
  - Stainless steel, Different sizes
  - Jacketed to allow for heating or cooling
  - Illumination for easy inspection
  - Built in agitation system for large volume mixing

...

3. Compounding procedure

- Diluted solutions for rapidly dissolving materials are simply prepared by adding the solute to solvent and agitating.
- For concentrated solutions or for slowly dissolving solutes application of heat may be required.
- The rate at which the solution is achieved markedly influenced by the compounding procedure.

...

- Solutes present in small concentration (dyes for example) should be predissolved before adding to the main portion of the batch.

- Complete solution should usually be confirmed at every stage in the manufacture of a homogeneous liquid.

  - It would be extremely difficult to determine the presence of a small amount of undissolved material at the bottom of the tank.

...

4. Packaging

- The method of **filling** is dependent on:
  - Nature of the liquid (viscosity, surface tension, foam producing quality, compatibilities)
  - Type of package
  - Required production out put

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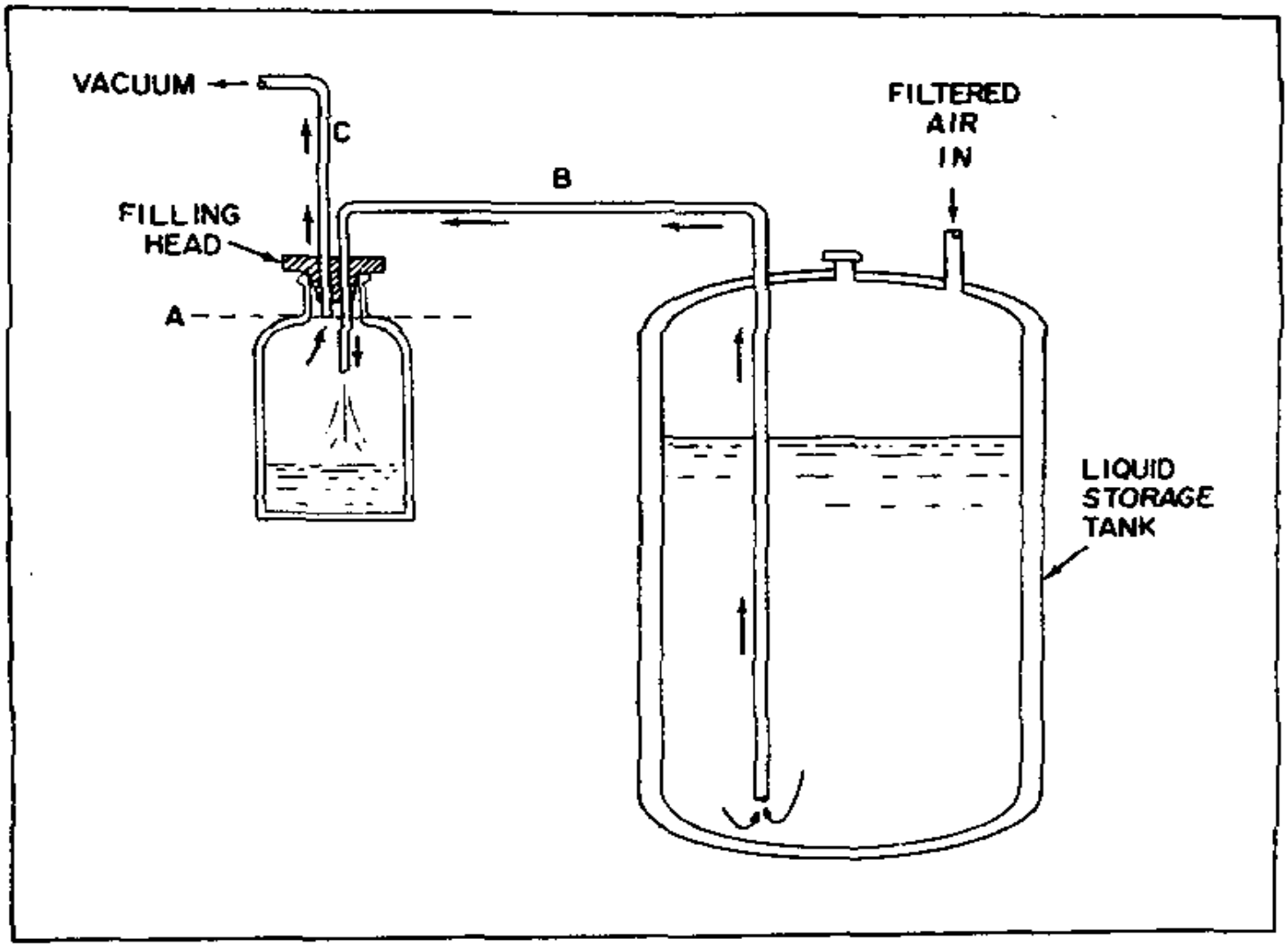
- 3 basic methods of filling
  1. Gravimetric method
  2. Volumetric method
  3. Constant level filling
- The second two methods are frequently used.

- Three categories/techniques for constant level filling:

1. Vacuum filling
2. Gravity vacuum
3. Pressure vacuum



Vacuum filling

Solutions, Quality Evaluations

- Reading assignment
  - Submit a short note not more than 3 pages

Pharmaceutical Suspensions

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- Almost all suspension systems separate on standing.
  - The main concern, therefore, is not necessarily to try to eliminate separation,
  - But, rather to decrease the rate of the settling and to permit easy resuspendability.
  - A satisfactory suspension must remain sufficiently homogeneous for at least the period of time necessary to remove and administer the required dose after shaking its container.

Theoretic Considerations

- Helps the formulator
  - To select the ingredients that are most appropriate for the suspension
  - To use the available mixing and milling equipment to the best advantage.

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Wetting

- A prime importance in suspension formulation concerns the wetting of the solid phase by the suspension medium.
- A good wetting of the suspended material is important in achieving a stable suspension.
- The contact angle shows degrees of wettability and indicates that surface properties are important.
- Based on affinity, suspended particles: Lyophilic or Lyophobic.

Particle Interactions and Behavior

- Non-wetting and wetting solids (?)
- The primary difference: their sensitivity to the presence of electrolytes.
- Lyophobic materials are sensitive to the addition of salts,
- Repulsive potential of the EDL and stability of particles (?)

...

- Flocculated and deflocculated systems (?)
- Open network aggregates (in flocculated systems)
  - The aggregates settle quickly to form a high sediment height.
  - These are easily redispersible because the particles constituting individual aggregates are sufficiently far apart from one another to preclude caking.
  - A clear supernatant is formed on settling.

...

- Closed aggregate,
  - Characterized by a tight packing produced by surface film bonding.
  - These aggregates settle slowly to low sediment heights that approach the sediment density of a dispersed particulate system.
  - Sediments are not easily redispersed.

...

- Sedimentation and aggregation rates are properties of suspension systems governed by
  - Particle size,
  - Particle-particle interactions,
  - Densities of the particles and the medium, and
  - The viscosity of the continuous phase.

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- Temperature changes that occur during shelf storage lead to unexpectedly rapid caking via crystal bridging.
- This process, known as Ostwald ripening, is unavoidable in pharmaceutical suspensions of the dispersed type.
- Caking via crystal bridging can be minimized by utilizing the open network aggregate (floccule) suspension type.

...

Sedimentation Rates

- Stokes relation describes the sedimentation velocity of a particle in suspension:

$$v = \frac{2r^2(d_1 - d_2)g}{9\eta} = \frac{D^2(d_1 - d_2)g}{18\eta}$$

where v = velocity of the sedimentation in cm/sec; r = particle radius and D particle diameter in cm; d1 and d2 = density of the particle and the liquid, respectively, in g/ml; g = gravitational constant 980.7 cm/sec, η the viscosity of the medium in poises

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- Pharmaceutical suspensions may not obey the Stokes equation
  - Concentrated (i.e., those containing more than 10 g of solid per 100 ml)
  - Hetero-dispersed particles (i.e., not all particles are the same size)
  - Irregularly shaped particles

...

Crystal Habit

- This defines as the outward appearance of an agglomeration of crystals.
- Crystal habit can be of great importance in suspension redispersibility, sedimentation, physical stability, and appearance.
- Agglomerate of the crystals can have physical properties vastly different from those of single crystals.

...

Crystal Structure Factors

- The way the particles of a suspension prepared is an important concern.
- Suspensions are prepared by either **dispersion** or **precipitation** techniques.
- These methods will have effect on initial or subsequent physical stability in the suspension.

...

- When there is no change in the crystal habit, the following factors may still be considered:
  - Drug decomposition leading to salting in or out,
  - pH changes,
  - Changes in the particle size distribution, and
  - The effect of change in temperature.

...

- When there is a change in crystal habit, **solvation** and **polymorphism** are of importance.
  - The rate of physiologic absorption can be greatly altered, depending on which crystalline or amorphous forms are administered.
- The type of inherent crystal form is determined by the factors that govern the rate of crystal growth.

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- Some of these factors:
  - The rate of cooling,
  - The extent and degree of agitation, and
  - The size and number of nuclei.
- Other important factors include pH, solvent effects, and perhaps most important, the impurities present.

...

- Crystal growth increases with an increase in particle solubility,
  - Excipients that increase the particle solubility should be kept to a minimum.
- Crystal growth also increased with stirring, since the mean free diffusion path of the solute molecules is reduced.
- Similarly, if sedimentation occurs the local increase in particle concentration increases particle growth.

Suspension Formation

Precipitation Methods

- Three precipitation methods:

1. Organic solvent precipitation
2. Precipitation effected by changing the pH of the medium
3. Precipitation by double decomposition

...

1. Organic solvent precipitation

- Water-insoluble drugs can be precipitated by dissolving them in water-miscible organic solvents and then adding the organic phase to distilled water under standard conditions.

- Examples of organic solvents used include ethanol, methanol, propylene glycol, and polyethylene glycol.

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- Several important considerations are involved when this method is used.
  - Particle size
  - Polymorphic form or hydrate of the crystal be obtained.
  - The solvent and solvent entrapment
  - Volume ratios of the organic to the aqueous phase

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- Rate and method of addition of one phase to the other
- Temperature control (cooling rate and drying conditions),
- Method of drying the precipitate (forced air, vacuum, or freeze drying),
- The washing of the precipitate.

...

2. Precipitation by changing pH of the medium

- More readily accomplished and does not present the same difficulties associated with organic solvent precipitation.
- But, the method is only applicable to those drugs in which solubility is dependent on the pH
  - E.g. Preparation of **Estradiol** and **Insulin** suspensions

...

- The type of crystal or polymorphic form depends on such factors as:
  - The concentrations of acid and base
  - The degree and type of fluid shear imparted to the system

...

- In both the above methods
  - The degree of supersaturation changes throughout the process, and
  - The rate of nucleation and the rate of crystal growth are not constant; therefore,
  - The particle size distribution is variable.

...

3. Precipitation by double decomposition

- This involves only simple chemistry

...

Dispersion Methods

- The vehicle must be formulated so that the solid phase is easily wetted and dispersed.
- The use of surfactants is desirable to ensure uniform wetting of hydrophobic solids.
- The use of suspending agents may be indicated.

...

- A number of dispersion methods are used to prepare suspension products.
  - The actual method of dispersing the solid is important considerations because particle size reduction may or may not result from the dispersion process.
  - The particles obtained may have different solubilities if a metastable state is involved,
    - This may lead to transient supersaturation of the system.

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Formulation of Suspensions

- Many factors must be considered in the course of developing a suspension dosage form.
- The basic concern involves the fact that suspensions settle, and it is necessary to redistribute them before using.

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- A desirable suspension should be:
  - Easily redispersed by shaking,
  - Remain suspended long enough to withdraw an accurate dose,
  - Have the desired flow properties.

...

- Aggregated or Deaggregated systems?
- A decision must be made as to the general type of suspension system desired.
  - Aggregated systems exhibit a minimum of serious separation, but, at times, an aggregated system may appear to be coarse because of the aggregates formed.
  - In dispersed systems, the particles are well distributed and settle singly but more slowly.
    - The particles, however, have a tendency to form a sediment or cake.

...

Rheologic Considerations

- Rheologic characteristics can be determining factor in the optimization of the physical stability of the suspension system.
- A suspension that possess **thixotropic** behavior is desirable.
  - A high viscosity at rest - prevent sedimentation
  - Agitation reduces the viscosity to permit pouring.

...

Formulation Adjuvants

- Preservative, color, and flavor may be included,
- Compatibility with the drug and vehicle is very important,
- Final packaging shall also be considered,
  - These factors include loss of flavor, preservative adsorption, and leaching into the product of substances from the container

Evaluation of Suspension Stability

- Test procedures involve:
    - Sedimentation volume
    - Rheologic Methods
    - Electrokinetic Techniques
    - Particle Size Changes (microscopic technique)
    - Dissolution studies

Pharmaceutical Emulsions

- An emulsion
  - As a thermodynamically unstable mixture of two essentially immiscible liquids (chemists).
  - As an intimate mixture of two immiscible liquids that exhibits an acceptable shelf life near room temperature (formulators).
  - It is almost universally accepted that the term emulsion should be limited to liquid-in-liquid systems.

- Emulsions are popular dosage forms:
  - Objectionable taste or texture
  - Absorption or bioavailability
  - Patient acceptance

...

Theories of emulsification (read more)

- **Droplet Stabilization**
  - By lowering the interfacial tension and/or by preventing the coalescing of droplets.
  - SAAs are capable of performing both objectives: they reduce interfacial tension, and they act as barriers to droplet coalescence.

- Emulsifying agents assist in the formation of emulsions by three mechanisms:
  - Reduction of interfacial tension – thermodynamic stabilization.
  - Formation of a rigid interfacial film – mechanical barrier to coalescence.
  - Formation of an electrical double layer – electrical barrier to approach of particles.

...

- **Emulsion type**
  - Various factors determine whether an o/w or a w/o emulsion will be produced:
    - The phase volume ratio
    - Type of the emulsifier
    - Mixing order
    - Viscosity of each phase

...

- **Microemulsions**
  - Dispersions of insoluble liquids in a second liquid that appear clear and homogeneous to the naked eye.
  - These are frequently called solubilized systems because on a macroscopic basis they seem to behave as true solutions.
  - These are believed to be thermodynamically stable.
  - Read more

Formation of Emulsions

- Emulsions cannot be formulated spontaneously.
- In the commonly employed dispersion method – two sequential processes involved:
  - Breaking up the internal phase into droplets and
  - Stabilizing them in the external phase

...

- Some physical and chemical parameters are selected and controlled to favor emulsion formation:
  - **Physical Parameters** – Heat, Phase Inversion Temperature, Timing, …
  - **Chemical Parameters** - Chemical Stability, Safety, Choice of the Lipid Phase, Phase Ratio, Choice of Emulsifying Agents, Choice of Surfactant, Choice of Auxiliary Emulsifiers

...

Physical Parameters

Heat

- It is possible to prepare emulsions by passing the vapor of a liquid into an external phase that contains suitable emulsifying agents (condensation method).

- Relatively slow, and is limited to the preparation of dilute emulsions of materials having a relatively low vapor pressure.

...

- Note the effect of temperature;
  - An increase in temperature decreases interfacial tension as well as viscosity, so that emulsification is favored.
  - An increase in temperature raises the kinetic energy of droplets and thereby facilitates their coalescence.
  - Changes in temperature alter the distribution coefficients of emulsifiers between the two phases and cause emulsifier migration.

...

Phase inversion temperature

- The temperature at which the inversion occurs, and it depends on emulsifier concentration.
- Phase inversion can occur during the formation of emulsions.
- Emulsions formed by a phase inversion technique are generally considered quite stable and are believed to contain a finely dispersed internal phase.

...

Timing

- During the initial period of agitation required for emulsification, droplets are formed.
- As agitation continues, the chance for collision between droplets becomes more frequent, and coalescence can occur.
- It is advisable, therefore, to avoid excessive periods of agitation during and after the formation of an emulsion.

...

Low-Energy Emulsification

- The classic process of emulsification (described above) requires considerable expenditure of energy.
- In low-energy emulsification, all of the internal phase, but only a portion of the external phase is heated.
- After emulsification of the heated portions, the remainder of the external phase is added to the emulsion concentrate

- Important variables to be controlled:
  - Emulsification temperature
  - Mixing intensity
  - Amount of the external phase employed during emulsification
  - Method of blending

...

- Various types of equipment are available to effect droplet breakup and emulsification.
  - Mechanical stirrers
  - Homogenizers
  - Ultrasonifiers
  - Colloid mills

...

- The degree of shear and turbulence required to produce a given dispersion of liquid droplets is important factor involved in the preparation of an emulsion.
- The amount of agitation required depends on:
  - The total volume of liquid to be mixed
  - The viscosity of the system, and
  - The interfacial tension at the oil-water interface.

...

1. Mechanical Stirrers

- Emulsion stirred by means of various impellers mounted on shafts, which are placed directly into the system to be emulsified.
- For low viscosity emulsions, propeller mixers are adequate.
- For more vigorous agitation, or if the preparation has moderate viscosity, turbine type mixers are employed.
- Other mixers, provided with paddle blades, counter rotating blades, or planetary action blades, are available for special requirements.

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- The degree of agitation is controlled by the speed of impeller rotation.
- But, the patterns of liquid flow and the resultant efficiency of mixing are controlled by:
  - The type of impeller,
  - The position the impeller in the container,
  - The presence of baffles, and
  - The general shape of the container

- The use of stirrers for the formation of emulsions is often limited
  - When vigorous agitation of viscous systems is required
  - When extremely fine droplets are needed
  - When foaming at high shear rates must be avoided

...

2. Homogenizers

- The dispersion of two liquids is achieved by forcing their mixture through a small inlet orifice at high pressures.
- It is possible to recycle the emulsion.
- Can handle either liquids or pastes (the rate of throughput is little affected by viscosity).
- Warranted when monodisperse emulsion of low particle size (1 nm) is required.

...

3. Ultrasonifiers

- Use ultrasonic energy.
- Have limited output and are relatively expensive.
- Useful for the laboratory preparation of fluid emulsions of moderate viscosity and extremely low particle size.

...

4. Colloid mills

- Operate on the principle of high shear, which is normally generated between the rotor and the stator of the mill.
- Primarily used for the comminution of solids and for the dispersion of suspensions containing poorly wetted solids
- Are also useful for the preparation of relatively viscous emulsions.

...

Spontaneous Emulsification

- Spontaneous emulsification occurs when an emulsion is formed without the application of any external agitation.
- E.g. formation of microemulsions
- This method is not practiced commercially.

...

Foaming during Agitation

- Foaming occurs because the water-soluble SAA required for emulsification generally also reduces the surface tension at the air-water interface.

- To minimize foaming,

  - Emulsification may be carried out in closed systems.

  - Add foam depressants (antifoams)

Chemical Parameters

- Chemical Stability
- Safety
- Choice of the Lipid Phase
- Phase Ratio
- Choice of Emulsifying Agents

- **Choice of Emulsifying Agents**
  - Three broad classes: Surfactants, the Hydrophilic colloids, and the Finely divided solids.
  - **Choice of Surfactant**
    - Anionic, Cationic, Amphoteric, or Nonionic
  - **Choice of Auxiliary Emulsifiers**
    - Finely divided solids: Polar inorganic solids (e.g. heavy metal hydroxides, non-swelling clays, and pigments), Nonpolar solids
    - Hydrophilic Colloids: Smectite Natural and synthetic clays (e.g. bentonites)

...

Formulation Considerations

Consistency

- A consistency that provides the desired stability and yet has the appropriate flow characteristics must be attained.

- Keeping other variables constant, an increase in viscosity generally minimizes creaming, rising, or sedimentation.

...

- Thixotropy in an emulsion is desirable.
- There is a linear relationship between emulsion viscosity and the viscosity of the continuous phase.
- The greater the volume of the internal phase, the greater is the apparent viscosity.
- The viscosity of emulsions increases upon aging.

...

Clear Emulsions

- Opaque Vs Clear emulsions
- The amount of internal phase in clear emulsions or in solubilized systems is generally lower than that in opaque emulsions.
- An increase in the surfactant concentration(s) reduces the opacity of all types of emulsions.

...

Choice of an Antimicrobial Preservative

- Presence of carbohydrates, proteins, sterols, and phosphatides support the growth of a variety of microorganisms.
- Presence of a mixture of lipid and water in intimate contact.
- Microbial contamination may occur during the development or production of an emulsion or during its use.

...

- Prevention of contamination is recommended.
  - Use of uncontaminated raw materials, including the water.
  - Meticulous housekeeping and careful cleaning of equipment.
- Requirements for an effective preservative???
- The preservative water-oil partition coefficient??
- Interaction of the preservative with one of the emulsion ingredients to be considered.

...

Choice of Antioxidant

- Emulsified lipids are particularly sensitive to attack by oxidation.
- Many drugs commonly incorporated into emulsions are subject to autoxidation and resulting decomposition.
- Antioxidants are commonly used at concentrations ranging from 0.001 to 0.1%.

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- Butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), L-tocopherol, and the alkyl gallates are popular antioxidants.

- Combinations of two or more antioxidants have been shown to produce synergistic effects.

Emulsion Stability

- Thermodynamic stability of emulsions differs from stability on the basis of subjective judgments.
- Acceptable stability in a pharmaceutical dosage form does not require thermodynamic stability.
- If an emulsion creams up or creams down, it may still be pharmaceutically acceptable as long as it can be reconstituted by a modest amount of shaking.

...

- Shelf life is a useful term to describe the subjective evaluation of stability.
- A product's shelf life may be directly related to its "kinetic" stability.
  - Kinetic stability ~ parametres do not change appreciably during a reasonably long period of time.
  - Thermodynamic stability ~ temperature dependent.

- Symptoms of instability (read more)
  - Creaming
    - Droplets tend to rise or sediment depending on the differences in specific gravities between the phases.
  - Flocculation
    - Reversible aggregation of droplets of the internal phase in the form of three-dimensional clusters.
    - An increase of the ionic strength with electrolytes or an increase of the emulsifier concentration, or a high internal phase volume tends to promote flocculation.

- Coalescence
  - A growth process during which the emulsified particles join to form larger particles.
  - May lead to eventual separation of the emulsion.

- Assessment of emulsion shelf life
  - Acceptable emulsion shelf life?
  - Predictive indicators of shelf life?
- Unequivocal and quantitative answers are required.
- No quick and sensitive methods for determining potential instability in an emulsion.
- Need to speed up stability program (stress), or need for tests more sensitive for the detection of instability

- Stress conditions: Aging and temperature, Centrifugation, Agitation
  - Aging and Temperature
    - A changes in temperature bring into play new reactions.
    - It is important to realize that exposure to unrealistically high temperatures may produce meaningless results.
    - Emulsions cannot tolerate temperatures in excess of 55 or 600 even for a few hours.

- Changes in temperature will have effect on: viscosity, partitioning of emulsifiers, Inversion at the phase inversion temperature, and crystallization of certain lipids.

- A particularly useful means of evaluating shelf life is cycling between two temperatures (between 4 and 45^{O}C).

- The normal effect of aging an emulsion at elevated temperature is acceleration of the rate of coalescence or creaming.

- Centrifugation

  - Separation of the dispersed phase due to either creaming or coalescence is accelerated when the emulsion is exposed to centrifugation.

  - Stokes' law shows that creaming is a function of gravity, and an increase in gravity therefore accelerates separation.

- Agitation
  - Simple mechanical agitation can contribute to the energy with which two droplets impinge upon each other.
  - Excessive shaking of an emulsion or excessive homogenization may interfere with the formation of an emulsion.
  - Agitation can also break emulsions.